Security Classification

DOCUMENT CONTROL DATA - R & D

Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified.

1. ORIGINATING ACTIVITY (Corporate author) Aerospace Medical Research Laboratory, Aerospace Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio 45433	2a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED 2b. GROUP N/A

3. REPORT TITLE

EXPERIMENTAL HUMAN EXPOSURE TO CARBON MONOXIDE <1 to 1000 PPM

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

5. AUTHOR(S) (First name, middle initial, last name)

Richard D. Stewart, M.D., M.P.H. — Edward D. Baretta — Terrance N. Fisher, M.D.
Jack E. Peterson, Ph.D. — Hugh C. Dodd — Anthony A. Herrman, M.D.
Michael J. Hosko, Ph. D. — Paul E. Newton

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
December 1970	27	10

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
F 33615-70-C-1046	AMRL-TR-70-102
8b. PROJECT NO. 6302	Paper No. 4
8c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
8d.	

10. DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
Conference was arranged by the Toxic Hazards Research Unit of SysteMed Corporation	Aerospace Medical Research Laboratory, Aerospace Medical Div., Air Force Systems Command, W-PAFB, Ohio 45433

13. ABSTRACT

This paper was presented at the Proceedings of the 1st Annual Conference on Environmental Toxicology, sponsored by the SysteMed Corporation and held in Fairborn Ohio on 9, 10, and 11 September 1970. Major technical areas discussed included toxicological evaluation of carbon monoxide, methodology, pathology, atmospheric contaminants, and toxicology of propellants and other military chemicals.

Key words:
Toxicology
Carbon Monoxide

DD FORM 1473

AMRL-TR-70-102

PAPER NO. 4

EXPERIMENTAL HUMAN EXPOSURE TO CARBON MONOXIDE < 1 TO 1000 PPM*

Richard D. Stewart, M. D., M. P. H.
Jack E. Peterson, Ph. D.
Michael J. Hosko, Ph. D.
Edward D. Baretta
Hugh C. Dodd
Paul E. Newton
Terrance N. Fisher, M. D.
and
Anthony A. Herrmann, M. D.

The Medical College of Wisconsin
Milwaukee, Wisconsin

As man grapples with the problems of air pollution in an attempt to establish air quality standards, he finds he possesses limited information regarding the biological effects of short-term and continuous exposure to low concentrations of carbon monoxide (CO). Only a few investigations have been conducted in which sophisticated instrumentation was used to search for minute changes in human performance induced by exposure to low concentrations of CO (McFarland et al, 1944; Schulte, 1963; Beard and Werthcim, 1967). Lacking is the information as to whether these minor alterations in function which have been reported are of any practical significance to the health, performance, or judgment of man as he performs his daily tasks.

EXPERIMENTAL PROCEDURE

In an attempt to gather additional human toxicological information about CO, a series of experimental exposures to known concentrations of the gas was conducted. These exposures were designed to simulate the type encountered for industry and in urban areas where CO is absorbed over a period of hours.

*Most of the information in this report has been published in the Archives of Environmental Health, 21:154-180, August, 1970.

Exposure Chamber

A room measuring 20 x 20 x 9 feet high served as the exposure chamber. The air flow through the room to the exhaust was 500 cu ft/min, which created a slight negative pressure within this chamber. Carbon monoxide was continuously metered into the chamber from a compressed gas cylinder in the adjacent command laboratory. The CO used was a chemically pure grade with a minimum purity of 99.5%.

The air-conditioned chamber featured pleasant lighting, comfortable chairs, and study desks. Activity within the chamber was strictly sedentary. Meals were served to the subjects during the exposures, and coffee and soft drinks were available on an ad lib basis. The subjects were under continuous visual surveillance by medical personnel while in the chamber. In addition, all chamber activities were visually monitored and video taped in the command laboratory by closed circuit TV.

Analysis of Exposure Chamber Atmosphere

The concentration of CO in the chamber atmosphere was recorded continuously by an infrared spectrometer equipped with a 10-meter pathlength gas cell which was continuously flushed with air drawn from the chamber through 1/4-inch diameter polyethylene tubing.

The chamber atmosphere was also monitored periodically by a gas chromatograph (GC) equipped with a helium ionization detector. Calibration standards of CO and air were prepared in saran bags and were analyzed by both the infrared and gas chromatographic methods before and every hour during each experiment.

Subjects

Twenty-eight healthy medical students and medical school faculty ranging in age from 24 to 42 years volunteered for the exposure studies. Only three were smokers, but they agreed to abstain from smoking for the duration of the study. Each was given a comprehensive medical examination which included a complete history and physical examination and the laboratory studies listed below.

Exposure Schedule

Table 1-A presents the exposure schedule and lists the concentration and duration for the first 25 experiments. Experiments 1 and 9 were control experiments. The CO concentrations in experiments 2 through 8 and 10 through 13 were selected at random so that neither the volunteers nor the investigators who conducted the testing procedures knew the concentration of CO on a given test day. The same group of subjects was in experiments 1 through 8 while a different group was studied in experiments 9 through 13. Two toxicologists from the medical school faculty were the subjects in experiments 22 through 25.

TABLE I-A

HUMAN EXPOSURE TO CARBON MONOXIDE

Experiment	No. of Subjects	CO Concentration, ppm Mean	SD	SE	Duration (hr)
1	8	< 1	...	...	8.0
2	7	< 1	...	...	8.0
3	8	26.4	1.2	0.20	8.0
4	7	103.2	6.9	0.90	8.0
5	8	24.8	1.3	0.20	8.0
6	7	1.6	0.3	0.04	8.0
7	8	49.4	7.5	0.90	8.0
8	7	98.0	2.8	0.40	8.0
9	4	< 1	...	...	8.0
10	4	< 1	...	...	8.0
11	4	94.0	5.7	0.7	8.0
12	4	< 1	...	...	8.0
13	4	99.8	6.0	0.8	8.0
14	9	51.6	0.5	0.2	1.0
15	6	51.2	1.0	0.2	3.0
16	3	50.3	1.5	0.2	8.0
17	3	49.9	1.8	0.2	24.0
18	10	99.7	2.1	0.8	1.0
19	6	98.1	2.4	0.5	3.0
20	2	100.2	3.2	0.4	8.0
21	11	199.5	9.9	1.6	4.0
22	2	507.0	17.3	3.5	1.8
23	2	494.0	25.4	3.4	2.3
24	2	473.3	27.4	3.6	2.3
25	2	598.0	Range:	1 ppm rising to 1000 ppm	

TABLE I-B

TIME DISCRIMINATION - TIME ESTIMATION EXPERIMENTS

Experiment	No. of Subjects	CO Concentration, ppm			Duration (hr)
		Mean	SD	SE	
26	8	100.99	4.28	0.54	5.0
27	8	50.64	3.83	0.54	5.0
28	8	196.49	3.00	0.41	5.0
29	8	< 2	...	...	5.0
30	8	49.82	2.36	0.31	5.0
31	7	201.38	6.58	0.95	5.0
32	4	4.44	0.76	0.06	24.0
33	6	< 2	...	...	5.0
34	7	99.81	3.77	0.77	2.5
35	8	96.13	4.39	0.62	5.0
36	6	203.69	6.39	1.33	2.5
37	4	< 2	...	...	24.0
38	8	< 2	...	...	5.0
39	4	24.36	2.24	0.17	24.0
40	6	< 2	...	...	2.5
41	6	49.45	1.43	0.27	2.5
42	6	201.70	4.21	0.72	2.5
43	6	< 2	...	...	2.5
44	6	49.67	3.56	0.66	2.5
45	4	99.93	1.66	0.31	2.5
46	2	201.72	6.94	1.36	2.5
47	2	192.90	5.85	1.15	2.5
48	2	< 2	...	...	2.5
49	2	< 2	...	...	2.5
50	2	< 2	...	...	2.5
51	2	< 2	...	...	5.0
52	2	193.1	33.4	2.6	2.5
53	2	197.7	9.56	1.69	2.5
54	2	< 2	...	...	2.5
55	6	192.3	21.4	3.5	5.0
56	2	199.96	2.97	0.56	2.5
57	2	< 2	...	...	2.5
58	2	< 2	...	...	2.5
59	5	196.98	8.66	1.69	5.0

Table I-B presents the exposure schedule for the series of experiments designed to investigate the effect of CO upon time estimation and time discrimination.

Clinical Testing

A preexposure venous blood sample was obtained for a complete blood cell count, sedimentation rate, sodium, carbon dioxide, chloride, potassium, calcium, total serum protein, alkaline phosphatase, bilirubin, blood urea nitrogen, glucose, serum glutamic oxaloacetic transaminase, and carboxyhemoglobin determination. This battery of blood tests was repeated 16 hours after each exposure to CO which featured concentrations of 100 ppm or greater. Baseline values for the following tests were obtained: hand and foot reaction time in the American Automobile Association (AAA) driving simulator, Crawford collar and pin test, Crawford screw test, hand steadiness in the AAA steadiness test, Flanagan coordination test, othorator visual test, complete audiogram, resting 12-lead ECG, standard electroencephalogram, visual evoked response (VER), 10-second time estimation, 30-second time estimation, Beard-Wertheim time discrimination test (Beard, 1967), and time estimation-hand reaction time test. Those subjects exposed to concentrations of CO in excess of 100 ppm had first to demonstrate a normal exercise ECG which monitored the effect of vigorous running in place for a three-minute interval. The orthorator visual test included an evaluation of far vision vertical and lateral phoria, far vision acuity, depth perception, color vision, near vision acuity, and near vision vertical and lateral phoria.

Each subject was given a repeat physical examination one hour before entering the exposure chamber. At this time he was queried as to whether he was experiencing headache, nausea, dizziness, abdominal pain, chest pain, eye, nose or throat irritation, or any other subjective symptom. Venous blood and alveolar breath samples for analysis completed the preexposure evaluation.

During the exposures, the subjective and objective responses of each individual were recorded during every waking hour. In experiments 1 through 13, physiological performance tests were periodically conducted and always within the final hour of CO exposure. In the remaining experiments, selected tests were performed. Venous blood samples for carboxyhemoglobin (COHb) and total hemoglobin analysis were obtained serially from each subject after he has passed his arm through a small sampling port in the exposure chamber into an uncontaminated atmosphere (figure 1, table II).

Following each exposure, serial venous blood samples were obtained in an adjacent contamination-free laboratory for COHb analysis. At the same time, alveolar breath samples were collected in saran bags, using the 20-second breath-holding technique for infrared analysis and in glass breath collection pipettes (Health Science Services, Brookfield, Wisconsin) for GC analysis (Stewart et al, 1965). All untoward subjective responses occurring in the first 24-hour postexposure interval were recorded.

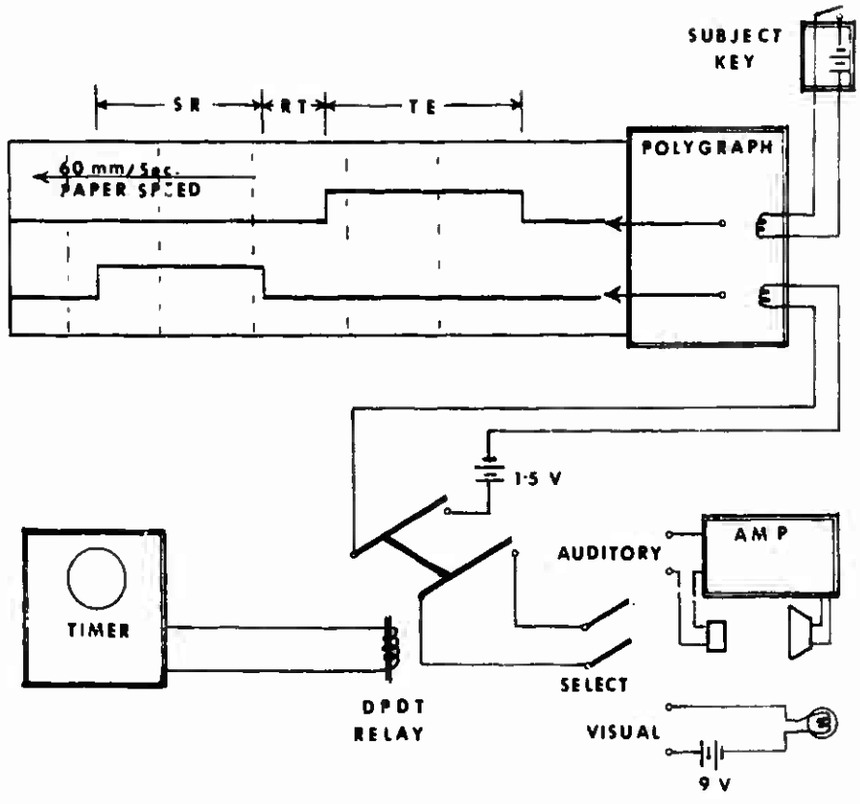

Figure 1. SCHEMATIC DIAGRAM OF REACTION TIME - TIME ESTIMATION APPARATUS. Stimulus Record (SR), Response or Reaction Time (RT), and Subjects Estimate of Stimulus Duration (TE). (Reprinted with permission from the Archives of Environmental Health, 21:156, August, 1970).

TABLE II

PERCENT OF COHB DURING AND FOLLOWING EXPOSURE TO 50 PPM OF CO

Time During Exposure	Mean	Range	No. of Subjects
Preexposure	0.7	0.4-1.5	11
30 min	1.3	1.3	3
1 hr	2.1	1.9-2.7	11
3 hr	3.8	3.6-4.2	10
6 hr	5.1	4.9-5.5	5
8 hr	5.9	5.4-6.2	5
12 hr	7.0	6.5-7.9	3
15½ hr	7.6	7.2-8.2	3
22 hr	8.5	8.1-8.7	3
24 hr	7.9	7.6-8.2	3
Time after 1 hour of exposure			
30 min	1.8	1.8	3
1 hr	1.7	1.6-1.8	3
2 hr	1.5	1.4-1.5	3
5 hr	1.1	1.0-1.1	2
Time after 3 hours of exposure			
30 min	3.7	3.4-3.9	3
1 hr	3.3	2.7-3.8	3
2 hr	2.7	2.3-3.0	3
Time after 8 hours of exposure			
30 min	5.6	5.1-5.9	3
1 hr	5.1	4.8-5.4	3
1 3/4 hr	4.0	...	3
11 hr	1.5	1.4-1.7	3
Time after 24 hours of exposure			
30 min	7.5	7.2-7.8	3
1 hr	6.7	6.4-7.1	3
2 hr	5.8	5.6-6.2	3

Performance Testing

Time Estimation: In experiments 1 through 13, the time estimation test was performed immediately upon entrance of the subjects into the chamber after four and seven hours of exposure. In exposures of shorter duration, the final test was conducted during the final 30 minutes of exposure. In experiments 26 through 59 the test was performed each hour. This test required approximately seven minutes to perform and consisted of a series of nine tone stimuli followed by nine light stimuli of approximately 1, 3 or 5 seconds' duration presented in a random sequence with three stimuli at each time interval. At the termination of the stimulus, the subject depressed a push button for that interval of time he estimated to be equal in length to the original auditory or light stimulus. This was a measure of his ability to estimate the duration of the stimulus.

Figure 1 is a schematic diagram of this testing apparatus. A PBM 0- to 15-second, synchronous, motor-driven interval timer was used to initiate this stimulus-response sequence. The interval timer energized the coil of a double-pole double-throw relay for a preselected stimulus period. The stimulus period randomly approximated intervals of 1, 3, and 5 seconds. One pole of the double-pole double throw relay was utilized to close a 1.5-v circuit to one pen of a polygraph (Grass Model 6 EEG). This circuit provided a record of the exact duration of the stimulus. The second pole of the relay was connected across a selector switch to provide either a visual or an auditory stimulus. The visual stimulus was the light from a 9-v flashlight bulb diffused through a polyethylene tube to provide comfortable viewing. The auditory stimulus was generated by inducing oscillation in a small transistorized power amplifier (Realistic No. 277-1240-Radio Shack). Oscillation was induced by placing a small crystal microphone close to the output speaker. The tone was keyed on and off by interrupting the speaker circuit. This method provided sharp, crisp, tone initiation and termination.

Each subject was provided with a small aluminum minibox which contained a 1.5-v cell in series with a push-button switch connected to a pen of the polygraph. The record of the stimulus response was recorded by means of the polygraph pen deflection, which could easily be read to the closest 10 msec.

In each case, the subject's estimate of the stimulus duration was divided by the actual stimulus duration to normalize the response. Then three replicate normalized responses for each stimulus type and duration were averaged to obtain a mean normalized response for that exposure. A grand normalized time estimate response was determined for each subject by averaging normalized responses over both types of stimulus and for all exposures to control concentrations.

Responses obtained during exposures to CO were treated in two ways. First, mean normalized responses for each subject were used to obtain an overall average and standard deviation for each type of stimulus and stimulus duration at each exposure duration. Each subject's mean normalized response was subtracted from his characteristic response, and differences were used to determine the paired t for that set of

stimulus and exposure parameters. Data are shown in table IV. Second, mean normalized response data were also used in regression analysis to determine whether exposure duration, CO concentration, stimulus type, or stimulus duration were correlated significantly with response. These data follow the previous data in table V.

Expt.	CO Conc. ppm	n*	Driving Simulator Mean	SD**	Paired t	r	Hand Steadiness Mean	SD**	Paired t	r	$t_{0.05}$	$r_{0.05}$
Control	2	34	35.3	7.58	...		48.6	9.18	...		...	
3	26.4	8	31.5	5.76	1.36		44.6	9.87	-2.32		2.31	
5	24.8	8	32.1	7.99	1.20		53.9	7.07	-2.64		2.31	
7	49.4	8	32.4	6.12	1.20		53.2	7.14	-2.64		2.31	
4	103.2	7	30.2	4.87	1.12		51.9	6.31	-1.33		2.36	
8	98.0	7	32.4	4.86	0.98		48.0	10.93	-1.12		2.36	
11	94.0	4	31.8	4.27	2.36		46.2	3.30	-2.40		2.78	
13	99.8	4	34.0	6.16	1.24	-0.197	48.0	3.89	-0.28	-0.028	2.78	0.220

*Number of subjects participating in specific experiments.

**Standard deviation.

Expt.	CO Conc. ppm	n*	Crawford Collar and Pin Mean	SD**	Paired t	r	Crawford Screw Mean	SD**	Paired t	r	$t_{0.01}$	$r_{0.05}$
Control	2	34	26.9	3.77	...		18.2	4.78	...		...	
3	26.4	8	27.6	5.29	-0.88		19.8	5.11	-1.68		3.36	
5	24.8	8	28.7	2.62	-1.60		19.4	5.76	-1.20		3.36	
7	49.4	8	32.9	3.98	-2.24		19.2	4.50	-1.20		3.36	
4	103.2	7	27.0	4.51	0.00		19.0	5.52	- .07		3.50	
8	98.0	7	31.5	4.66	-0.49		19.8	5.17	- .07		3.50	
11	94.0	4	28.3	2.66	-0.88		20.1	4.50	-1.88		4.60	
13	99.8	4	21.0	3.32	-3.84	-0.251	19.6	2.50	-1.68	-0.106	4.60	0.220

TABLE IV

INFLUENCE OF CO EXPOSURE ON TIME ESTIMATION TEST

Experiment	CO Concentration ppm	Exposure During Hours	Type	Stimulus Duration, sec	n*	Normalized Time Estimate Mean	SD**	Paired t	$t_{0.05}$
Control	< 2	All	All	All	414	0.67	0.101	...	...
7	39.6	0.1	Tone	1	8	0.71	0.101	- .64	2.36
			Tone	3	...	0.59	0.044	.64	
			Tone	5	...	0.63	0.045	- .24	
			Light	1	...	0.62	0.061	.32	
			Light	3	...	0.63	0.041	.16	
			Light	5	..	0.59	0.071	.64	
7	49.0	7	Tone	1	8	0.65	0.149	0	2.36
			Tone	3		0.75	0.079	- .08	
			Tone	5		0.62	0.133	.24	
			Light	1		0.66	0.181	- .08	
			Light	3		0.60	0.158	.40	
			Light	5		0.59	0.135	.56	
11	90.3	0.5	Tone	1	4	0.57	0.127	0.96	3.18
			Tone	3		0.59	0.065	0.84	
			Tone	5		0.65	0.050	0.12	
			Light	1		0.62	0.101	0.48	
			Light	3		0.61	0.136	0.52	
			Light	5		0.57	0.128	1.44	
13	98.0	0.5	Tone	1	4	0.59	0.115	.72	3.18
			Tone	3		0.57	0.050	.32	
			Tone	5		0.61	0.045	0.64	
			Light	1		0.60	0.105	0.64	
			Light	3		0.70	0.048	-0.40	
			Light	5		0.62	0.085	0.44	

TABLE IV (Cont'd)

Experiment	CO Concentration ppm	Exposure During Hours	Type	Stimulus Duration, sec	n*	Normalized Time Estimate Mean	SD**	Paired t	$t_{0.05}$
8	98.2	4	Tone	1	7	0.66	0.137	.49	2.45
			Tone	3		0.67	0.066	.42	
			Tone	5		0.65	0.041	.56	
			Light	1		0.69	0.109	.35	
			Light	3		0.64	0.063	.63	
			Light	5		0.57	0.162	1.33	
11	94.4	8.6	Tone	1	4	0.56	0.075	1.48	3.18
			Tone	3		0.58	0.150	0.92	
			Tone	5		0.64	0.022	0.28	
			Light	1		0.64	0.147	0.12	
			Light	3		0.60	0.047	1.00	
			Light	5		0.62	0.000	0.48	
8	98.2	7	Tone	1	7	0.72	0.101	.07	2.45
			Tone	3		0.57	0.126	1.05	
			Tone	5		0.64	0.066	.33	
			Light	1		0.61	0.151	0.77	
			Light	3		0.69	0.064	0.20	
			Light	5		0.62	0.125	0.77	
13	99.8	9	Tone	1	4	0.61	0.155	0.36	3.18
			Tone	3		0.60	0.047	0.72	
			Tone	5		0.63	0.040	0.40	
			Light	1		0.70	0.141	-0.36	
			Light	3		0.71	0.040	-0.48	
			Light	5		0.61	0.138	0.48	

* Number of subjects participating in specific experiments.

** Standard deviation.

Ten- and Thirty-Second Time Estimation: In experiments 26 through 59 immediately upon entering the chamber, then hourly, each subject depressed a push button for an interval he estimated to be 10 seconds. This was repeated twice, then he estimated 30 seconds three times.

Beard-Wertheim Time Discrimination Test: In experiments 26 through 59 this test was performed immediately following the time estimation test. In experiments 26 through 45 the test was performed in a group setting while in the remainder of the experiments the subject was isolated either in the exposure chamber or in an audiometric booth to duplicate Beard's original conditions.

Reaction Time: The AAA driving simulator is a reaction-time testing device. A subject seated at a console is presented with one of three stimuli to which he must respond by turning his steering wheel right or left, or by removing his foot from the accelerator pedal and depressing the brake. Each of the stimuli are presented in a random but unvarying sequence. The time between stimulus and response for the 15 trials is automatically totaled by an accumulative timer.

Steadiness: The hand steadiness test is another AAA tester consisting of a gradually narrowing V-shaped vertical slot. A metal wand, held in one hand, is passed down the slot until one of the sides is touched. At this point, a light flashes, and the position of the wand is recorded. Scoring is tabulated by totalling the results of five trials.

Manual Dexterity: The Crawford collar and pin and the Crawford screw tests are measures of manual dexterity. Both tests give quite consistent results when learned and are easily administered. The Crawford collar and pin test requires the subjects to pick up a pin, about 5/8 of an inch long and approximately the same diameter as a paper clip, with forceps, place the pin upright in a hole, and ring the pin with a loosely fitting collar. The Crawford screw test requires the subject to pick up a short screw and drive it all the way through a threaded hole with a screwdriver. Both tests are scored on the basis of the number of tasks completed in three minutes.

Results of the driving simulator, hand steadiness, and the Crawford tests were all evaluated in a manner analogous to the time estimation tests. The latter tests, however, were only conducted once during each exposure at about seven hours into the exposure period. Results of these tests are also listed in table III.

Electroencephalogram and Evoked Response: The exposure chamber contained a copper screen-shielded cage with approximately 45 sq ft of floor area. Within this cage, an upholstered reclining chair with a back high enough to give support to the head and neck was used for EEG and evoked potential recording. Provocative procedures, including a short period of hyperventilation and photic driving, were included in the initial EEG examination.

Analysis of Breath and Blood for Carbon Monoxide

Five milliliter aliquots of venous blood were collected in vacutainer tubes containing ethylenediaminetetraacetic acid. The blood was immediately analyzed by two methods. The hemoglobin concentration and the COHb percentage were determined directly in a CO-Oximeter (Instrumentation Laboratories, Inc.). The second analytical method consisted of measuring the CO liberated from the COHb moiety, using a GC equipped with a helium ionization detector (H. C. Dodd et al, unpublished data). Alveolar breath samples were analyzed directly by infrared spectroscopy (Stewart et al, 1965) and by the GC method (H. C. Dodd et al, unpublished data).

RESULTS

Carbon Monoxide: 25, 50, and 100 ppm

No untoward subjective symptoms or objective signs of illness were noted during or in the 24-hour period following the exposures to 25, 50, and 100 ppm of CO. All of the clinical chemistries, including the repeat battery 16 hours following the 100 ppm or greater gas exposures, remained within the limits of normal. There was no detectable change from control values for the clinical tests listed under Experimental Procedure. Data for those tests judged to be most critical to the discussion are presented in tables III to V.

The only significant relationship was that of the Crawford collar and pin test versus CO concentration. In this case, the correlation coefficient, r, was significantly different from zero at the 0.05 level, indicating a decrease in the score with an increase in CO concentration. Two facts indicate that the apparent correlation was spurious. First, none of the paired t-tests for the pin and collar task even approached significance. Second, a similar task, the Crawford screw test, exhibited no correlation of score with CO concentrations.

For each concentration studied there was little individual variation in the absorption and excretion of CO, as reflected in the venous blood COHb concentration of the subjects. The COHb concentration was so predictable and reproducible for sedentary males from one experiment to the next that it could be expressed mathematically as a function of exposure time and concentration, as detailed in a companion article (Peterson and Stewart, 1970). The COHb data for the 50 and 100-ppm experiments are displayed in figure 2 and table II so that the concentration time relationship may be related to the performance data.

A predictable mathematical relationship was observed to exist between the postexposure alveolar-breath CO concentration and the postexposure venous COHb concentration. This relationship is detailed in a second companion article (Peterson, 1970).

TABLE V

REGRESSION ANALYSIS OF TIME ESTIMATION DATA

	n*	Correlation Coefficient	$r_{0.05}$
Concentration vs tone time estimate, < 3-hour exposure	21	-0.338	0.433
Concentration vs light time estimate, < 3-hour exposure	21	-0.128	0.433
Concentration vs tone time estimate, > 3-hour exposure	30	-0.247	0.361
Concentration vs light time estimate, > 3-hour exposure	30	-0.122	0.361
Stimulus duration vs tone time estimate, any exposure	51	-0.072	0.276
Stimulus duration vs light time estimate, any exposure	51	-0.191	0.276

* Number of subjects participating in specific experiments.

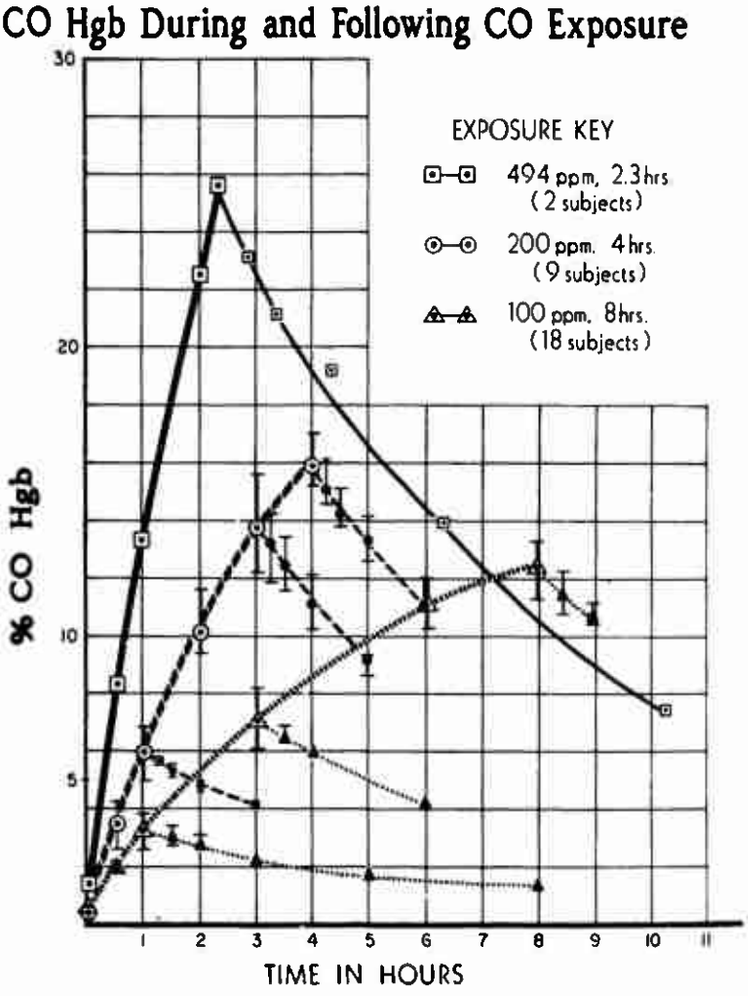

Figure 2. CARBON MONOXIDE ABSORPTION AND EXCRETION IN HEALTHY, SEDENTARY, NONSMOKING, WHITE MEN. (Reprinted with permission from the Archives of Environmental Health, 21:161, August, 1970).

Carbon Monoxide: 200 ppm, One to Four Hours

The three subjects exposed for four hours each reported that they had developed a "mild sinus" headache in the final hour. For one subject, this headache remained mild in intensity, subsiding completely in two hours. In the other two, headaches vanished during the first 30 minutes following exposure.

All of the clinical chemistries, including the repeat battery 16 hours postexposure, remained within the limits of normal. There was no detectable or statistical change from control values for the other clinical tests. The absorption and excretion of CO, as reflected in the venous blood COHb concentration of the subjects, are shown in figure 2.

There was no impairment noted in any of the performance tests. The Beard-Wertheim time discrimination test and the 10- and 30-second time estimation tests were initially performed in a group setting with twenty subjects divided into three separate groups for the random exposures to < 2, 50, 100, and 200 ppm. There was no detectable impairment in performance as a result of CO exposure. Using the paired t-test, the following t-values were calculated.

BEARD-WERTHEIM TEST IN GROUP SETTING

			After 2-hour exposure
$Group_{<2}$	vs.	$Group_{50}$	$t = 0.2700$
$Group_{<2}$	vs.	$Group_{100}$	$t = 0.3724$
$Group_{<2}$	vs.	$Group_{200}$	$t = -0.7567$

$n = 14$ Critical $t_{.01} = 2.779$

10-SECOND TIME ESTIMATION TEST IN GROUP SETTING

			After 2-hour exposure
$Group_{<2}$	vs.	$Group_{50}$	t = 0.9647
$Group_{<2}$	vs.	$Group_{100}$	t = 0.1345
$Group_{<2}$	vs.	$Group_{200}$	t = -0.2098

n = 14 Critical $t_{.01}$ = 2.779

30-SECOND TIME ESTIMATION TEST IN GROUP SETTING

			After 2-hour exposure
$Group_{<2}$	vs.	$Group_{50}$	t = 0.8945
$Group_{<2}$	vs.	$Group_{100}$	t = 0.3170
$Group_{<2}$	vs.	$Group_{200}$	t = 0.7786

n = 20 Critical $t_{.01}$ = 2.740

Beard's subjects were isolated in an audiometric booth during their exposures and testing while our subjects were exposed and tested in a group situation. To investigate the significance of this difference four subjects were reexposed in a double blind experiment to ambient and 200 ppm CO concentrations while in an isolated situation - alone in the 20 x 20 x 8 foot exposure chamber or in an audiometric booth. Performance while isolated in the audiometric booth or in the large chamber was not statistically different from that as a member of a group.

Using the paired t-test, the following t values were calculated:

$\text{Group}_{<2}$	vs.	$\text{Isolated}_{<2}$	$t = -1.135$
Group_{200}	vs.	Isolated_{200}	$t = 0.364$
$\text{Alone}_{<2}$	vs.	$\text{Booth}_{<2}$	$t = -0.000$
Alone_{200}	vs.	Booth_{200}	$t = -0.491$
$\text{Isolated}_{<2}$	vs.	$\text{Booth}_{<2}$	$t = -2.121$
Isolated_{200}	vs.	Booth_{200}	$t = 0.193$

$n = 4$ Critical $t_{.01} = 5.48$

Carbon Monoxide: 500 ppm

During the first exposure to 500 ppm of CO (experiment 22), one subject reported light-headedness after only 20 minutes of exposure. This was believed due to hyperventilation and persisted for 45 minutes. After one hour of exposure, both subjects were aware of a 10% increase in heart rate with the minimal exertion of walking to the blood sampling port. Ninety minutes into the exposure, the second subject noted the onset of mild frontal headache. Oxygen was administered by face mask immediately following the exposure, and within 10 minutes the second subject's headache was gone.

During the second exposure to 500 ppm of CO (experiment 23), the same subjects both developed mild frontal headaches after one hour of exposure. Minimal exertion caused a transient intensification of the pain. Both headaches remained mild during the first postexposure hour, then they intensified into excruciatingly severe occipitofrontal headaches, reaching a pain peak three and a half hours after exposure. These featured mild nausea, were not ameliorated by aspirin, and persisted for seven hours.

During the third exposure to 500 ppm of CO (experiment 24), the occurrence of mild frontal headaches again was noted after one hour of exposure. Immediately following the exposure, both subjects were placed in a hyperbaric chamber and administered oxygen at 3 ATA. The mild headaches were gone before the chamber was fully pressurized.

During experiment 25, the subjects were exposed to a constantly rising concentration of CO until a concentration of 1,000 ppm was reached after two hours. This peak concentration was then maintained for an additional 30 minutes. At the two-hour exposure mark, both subjects reported the presence of mild frontal headaches. Following the exposure, headaches became moderately severe over the first two postexposure hours. Six hours postexposure, the headaches were incapacitatingly severe and not ameliorated by aspirin. Twelve hours postexposure, after a night's sleep, the headaches were still noticeable.

All of the clinical chemistries, including the repeat-battery 16 hours postexposure, remained normal. Electrocardiograms taken at the conclusion of each experiment revealed no abnormalities. In experiments 23 and 24, a transient 10% increase in pulse rate was recorded every 15 minutes when the subjects would run in place for 15 seconds, but this was not different from the preexposure control values.

As the COHb saturation approached 20%, changes were observed in the VER. There was an increase in the amplitude of the 2-3-4 wave complex and a negative-going shift in the 5b and 5c segment. These changes increased as the saturation increased and promptly reverted to normal when COHb saturation fell below 15%.

In experiment 25, a series of control values for the two subjects for the Crawford collar and pin test were 33.5 ± and 40 ± 1. Five minutes before the end of the exposure, this test was repeated. Both subjects reported marked fatigue of hands and fingers while doing the test, and performance scores skidded dramatically to 29.5 and 32. One and one-half hours postexposure, the values were 33.5 and 38.5; hand fatigue was not noted.

The hand reaction time-time estimation test was also performed in experiment 25, 15 minutes before the conclusion of the exposure and again two hours postexposure. These data are presented in table VII and indicate a slight increase in reaction time two hours postexposure but no impairment of time estimation ability.

COMMENT

These experiments were conducted to obtain additional human toxicological information about CO over a range of carefully controlled concentrations. The low concentrations and the long durations of exposure which were chosen are those which may be encountered in urban and industrial settings. The brief exposures to high gas concentrations were included so that sufficiently high COHb saturations could be achieved which would result in untoward subjective responses and impairment of the subject's ability to perform the clinical tests.

TABLE VI

MEAN PERCENT OF COHb SATURATION

	Experiment 22	Experiment 23	Experiment 24	Experiment 25
Pre-exposure	0.6	1.5	1.2	0.4
Exposure time	...	...	...	...
15 min	5.3	...	...	1.2
30 min	9.2	8.2	8.0	2.1
45 min	...	...	...	3.7
1 hr	16.6	13.7	13.1	6.4
1¼ hr	...	...	...	9.8
1½ hr	...	18.4	18.1	14.3
1 3/4 hr	23.8	...	...	17.9
1.9 hr	24.8	...	...	...
2 hr	...	22.6	21.9	23.0
2¼ hr	...	25.4	...	28.1
2½ hr	...	...	...	31.8

Post-exposure time	100% O_2 by mask		O_2 at 3 ATA	
10 min	23.0		13.2	
15 min	...		...	30.3
30 min	19.6	23.1	7.6	28.5
1 hr	...	21.1	...	25.6
1¼ hr	13.9	...	...	...
2 hr	...	19.3	...	20.2
2¼ hr	...	...	...	18.4
3⅓ hr	...	...	...	15.6
4 hr	...	13.8	...	...
4½ hr	...	...	...	13.3

TABLE VII

HAND REACTION TIME - TIME ESTIMATION TEST

Experiment 25

Stimulus	Duration (sec)	Reaction Time (sec)	Time Estimate (E/D)*
Pre-exposure			
Tone	1	0.14	0.61
Tone	3	0.15	0.70
Tone	5	0.14	0.67
Light	1	0.17	0.68
Light	3	0.16	0.67
Light	5	0.16	0.64
Exposed 2.3 hours			
Tone	1	0.18	0.58
Tone	3	0.19	0.68
Tone	5	0.15	0.68
Light	1	0.19	0.61
Light	3	0.17	0.61
Light	5	0.15	0.68
2 hour post-exposure			
Tone	1	0.25	0.71
Tone	3	0.18	0.64
Tone	5	0.14	0.69
Light	1	0.21	0.56
Light	3	0.19	0.64
Light	5	0.14	0.66

*Actual duration.

The most important finding was that an eight hour exposure to 100 ppm of CO, resulting in a COHb saturation of 11% to 13%, produced no impairment of performance in the tests studied in this select, healthy group of volunteers. The tests chosen for investigation were those felt to be of practical significance in the performance of vocational endeavors and of automobile driving where significant impairment of visual or auditory acuity, coordination, reaction time, manual dexterity, or time estimation would be intolerable. The effect of exposures to 100 ppm of CO for eight hours on persons with preexisting cardiopulmonary diseases, on those consuming alcohol or central nervous system depressant drugs, and on the aged remains to be determined.

The subtlest effect of very small increases in COHb has been described by McFarland and his collaborators (1944). Visual brightness discrimination was impaired significantly when an increase of 4% COHb saturation had occurred. Conflicting reports are in the literature regarding the effects of small increments of COHb on flicker fusion frequency (Lilienthal and Fugitt, 1946; Vollmer, 1946). The significance of these subtle alterations in vision to those in various vocations remains to be defined. In our series of experiments, no significant impairment of those parameters of vision studied occurred as a result of eight hours of exposure to concentrations of CO as high as 100 ppm.

Schulte studied the effect on middle-aged firemen of exposure to 100 ppm of CO for varying periods of time (1963). The majority of his subjects were smokers. Included was a battery of psychomotor tests, and for some of these which tested cognitive abilities and choice discrimination, he reported variations in performance at COHb saturation concentrations below 5%. Reaction time, static steadiness, and muscle persistence were not altered by concentrations of COHb up to 20%. However, the very high COHb concentrations reported after exposures to only 100 ppm raises the question of reliable analytical techniques. Nonetheless, Schulte's observations regarding the adverse effect of CO on cognitive abilities and choice discrimination merit further investigation.

Beard and Wertheim (1967) have reported a distinct disturbance in the ability of healthy subjects to perceive differences in the duration of auditory stimuli following a 90-minute exposure to CO in concentrations as low as 50 ppm. (Carbon monoxide exposures of this magnitude for this duration would result in an increase of COHb saturation of approximately 2% above baseline). They further reported that decrement in performance increased dramatically with CO exposures of greater magnitude. We were unable to confirm these observations during exposures to CO in a group setting.

Our initial study to investigate the influence of the audiometric booth and isolation as a factor indicated that neither is a significant factor. While the "n" of four was small, it was large enough to detect the dramatic impairment in both time estimation and discrimination reported by Beard and Wertheim. This series is being enlarged to rule out the possibility of overlooking a CO effect much more subtle than that reported by Beard.

There were additional differences between the tests of Beard and our own. The difference of gravest concern was that Beard's tests were single blind studies, while ours were double blind. Beard and Wertheim's subjects were confined in a small audiometric booth which featured a black interior and no temperature or humidity control. Their chamber CO monitoring was done with a single non-dispersive infrared spectrometer in contrast to the multiple, independent monitoring systems here described. Beard and Wertheim report that they did not run CO standards from within their booth to their infrared instrument and that they were not able to analyze preexposure and post-exposure blood samples for COHb (1967). Without knowledge of subject COHb saturation, there is no second check on the magnitude of their CO exposures.

In our study, the ability of subjects to estimate time intervals of 1, 3, 5, 10, and 30 seconds was not impaired by CO exposures which resulted in COHb concentrations several fold higher than those which should have been encountered by Beard and Wertheim. The authors consider these time-estimation data of sufficient value that data from experiments 6-8, and 11-13 have been included in tables III to V. The difference between our findings and those of Beard and Wertheim merits resolution if the effect of CO absorption on time sense is to be known.

Those exposures which increased the COHb saturation to 20% or greater produced both subjective and objective evidence of CO intoxication. The first consistently present symptom of illness was the onset of a barely perceptible frontal headache occurring after the COHb saturation rose above 15% to 20%. An observation of clinical concern was that the severe headache of CO intoxication was a delayed phenomenon in the sedentary subject. It was apparent that exposure to a potentially lethal concentration of CO over a period of a few hours might occur without producing good warning symptomatology. It was also of interest to observe that the prompt administration of oxygen before the headache of CO became intense would quickly abolish all head pain.

As COHb saturation approached 20%, changes were observed in the VER. These changes became more marked as the COHb saturation neared 30%. The VER was the most sensitive objective indicator of CO effect.

The only time a manual dexterity test was performed when the subjects were grossly overexposed was in experiment 25, when the COHb saturation was 28%. Dramatic impairment of this function was observed. Following the exposure, but when the COHb saturation was approximately 22%, manual dexterity appeared normal. This suggests that significant impairment of manual dexterity could occur before a subject would otherwise be aware of CO intoxication.

In these experiments, the accuracy of the CO and COHb determinations is considered to be reliable because the analyses were performed by two independent methods. The breath CO was analyzed by infrared and by GC (H. C. Dodd et al, unpublished data) while the COHb was determined by the GC method and by the CO-Oximeter. The ability to confirm each blood and breath CO concentration during and following exposures to known CO concentrations provided the data with which to mathematically express the absorption and excretion of CO by these subjects. These regression equations are detailed in a companion article (Peterson and Stewart, 1970).

A second dividend from the accurate analyses of blood and breath was the opportunity to mathematically express the exponential relationship between venous blood and COHb concentration and alveolar breath CO concentration. This is discussed in detail in a second companion article (Peterson, 1970).

REFERENCES

1. Beard, R. R. and G. A. Wertheim; "Behavioral Impairment Associated with Small Doses of Carbon Monoxide"; Am. J. Public Health, 57:2012:2022, 1967.

2. Beard, R. R. and G. A. Wertheim; "Behavioral Manifestations of Carbon Monoxide Absorption"; Presented at the 16th International Congress on Occupational Health, Tokyo, September 25, 1969.

3. Hosko, M. J.; "Effect of Carbon Monoxide Exposure on the Spontaneous Electroencephalogram: And the Visual Evoked Response in Man"; Arch. Environ. Health, 21:174-180, 1970.

4. Lilienthal, J. L., Jr., C. H. Fugitt; "The Effect of Low Concentrations on the Altitude Tolerance of Man"; Am. J. Physiol., 145:359-364, 1946.

5. McFarland, R. A., F. J. W. Roughton, M. H. Halperin et al; "The Effects of Carbon Monoxide and Altitude on Visual Thresholds"; J. Aviation Med., 15:381-384, 1944.

6. Peterson, J. E. and R. D. Stewart; "Absorption and Elimination of Carbon Monoxide by Inactive Young Men"; Arch. Environ. Health, 21:165-171, 1970.

7. Peterson, J. E.; "The Post-Exposure Relationship of Carbon Monoxide in Blood and Expired Air"; Arch. Environ. Health, 21:172-173, 1970.

8. Schulte, J. H.; "Effects of Mild Carbon Monoxide Intoxication"; Arch. Environ. Health, 7:523-530, 1963.

REFERENCES (Cont'd)

9. Stewart, R.D., H.C. Dodd, D.S. Erley et al; "Diagnosis of Solvent Poisoning"; J. Am. Med. Assoc., 913:1097-1100, 1965.

10. Vollmer, E.P. et al; "The Effects of Carbon Monoxide on Three Types of Performance at Simulated Altitudes of 10,000 and 15,000 Feet"; J. Exp. Psychol., 36:244-251, 1946.

DISCUSSION

MR ADAMS (School of Aerospace Medicine): You made reference to cardiac output, now how did you measure this?

DR. STEWART (The Medical College of Wisconsin): We did this indirectly using the impedance cardiogram technique. We feel that this is a very reproducible, good way to measure cardiac output by a noninvasive method. It allows you to very nicely compare the individual with himself from setting to setting.

DR. ROBERTSON: You mentioned that females had a more rapid uptake and excretion of CO. Would you hypothesize why?

DR. STEWART: Yes, they breathe slightly differently than do the males. It is particularly obvious when we let them do a little exercise where we keep the exercise constant where the male might be a little more able to perform a given workload. A lighter female at the same workload breathes a little harder but we see then a more rapid uptake and a more rapid excretion.

DR. BEARD: Dr. Stewart, in your comparisons of performance, have you compared the subject against his own performance without carbon monoxide, or have all of the comparisons been based on group means?

DR. STEWART: We analyzed the data in several fashions. We have done it using group means, we have done it using the individual, using paired "T" tests, and in no instance have we found any CO effects.

DR. SALTZMAN (University of Cincinnati): From your work would you conclude, in an ordinary case where humans are exposed to fluctuating concentrations of carbon monoxide, that the only significant exposures of concern are the spikes, brief peaks, and I assume that this would be a matter of even a minute or two--would you regard this as a fair conclusion from your work?

DR. STEWART: I haven't gone that far in my thinking. I think the rate at which carboxyhemoglobin builds up in the blood stream may well be a very critical factor. I think that so far as the heart is concerned, it seems exquisitely sensitive to this change in rate of buildup. I think so far as effect upon central nervous system is concerned, that when all of the work has ultimately been completed, we will find there is a difference in performance at whatever level we begin to find CNS effects while one is ascending to equilibrium and once one gets at equilibrium. For example in our

manual dexterity tests, when we were at 30% saturation, I was one of the subjects and found it very difficult to use forceps and do the Crawford "collar and pin test", which is my one claim to fame, it is the one area in which I can outperform the medical students--they beat me in every other regard, arithmetic, reaction time--I guess I'm getting old and breaking down. I noted that one of the reasons I was having great difficulty was because every time I would move my hand my muscles would ache in hands and arms. So the manual dexterity was somewhat impaired probably because of anoxia. Now I didn't know what would happen if I were to be maintained at 30% saturation--how well I might adapt. I have a feeling that I would have got quite well, if my heart would permit it, and that I might then later be able to perform that test quite well, so I think that there is a rigorously acute exposure and the same type of exposure allowing one to work at equilibrium.

DR. HODGE: Thank you very much, Dr. Stewart.

DR. BEARD: May I ask one more question, Dr. Hodge?

DR. HODGE: Yes, Dr. Beard.

DR. BEARD: What nature of motivation was driving your subjects, was there anything beyond their inherent desire to do well?

DR. STEWART: In all the group settings, there was among the medical students that we chose, that same competitiveness that I think kind of characterizes the breed. In the individual setting we tried to simulate exactly what you have done and we gave them the same monetary motivation, $2.50 an hour during exposure for us to get rid of that variable, but otherwise we tried to duplicate in our setting as nearly as possible what we had photographed when you had graciously hosted our visit to your facility.